



6541620

Inventor: Brewer et al.
SN 08/484,337
Title: Tumor Necrosis Factor (TNF)
Inhibitor and Method for Obtaining Same
Application/Docket: 99,369
Group Art Unit: 1647

FIG. 1

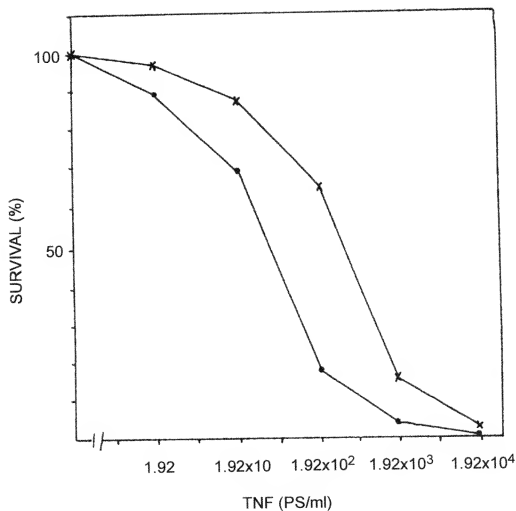
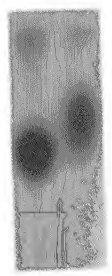


FIG. 2

b a (-)



(+)

FIG. 3

a b c d

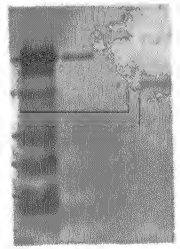


FIG. 4

a b c d



FIG. 5

a b

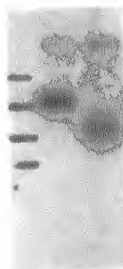
kDa

43

29

18

14





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FIG. 6A

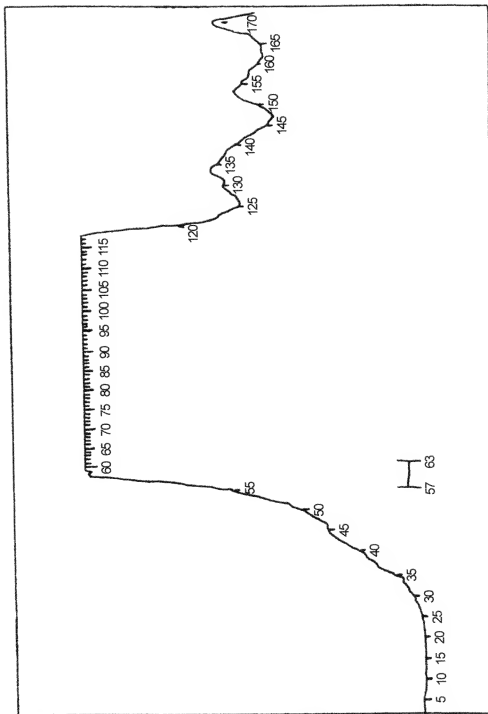
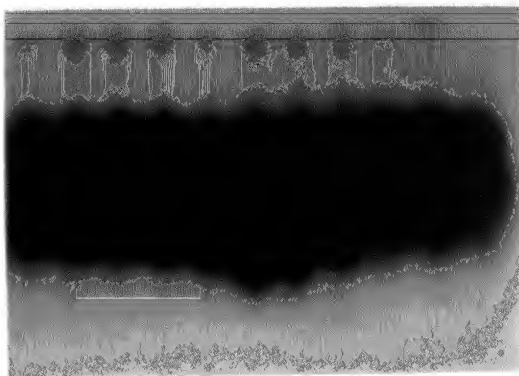


FIG. 6B

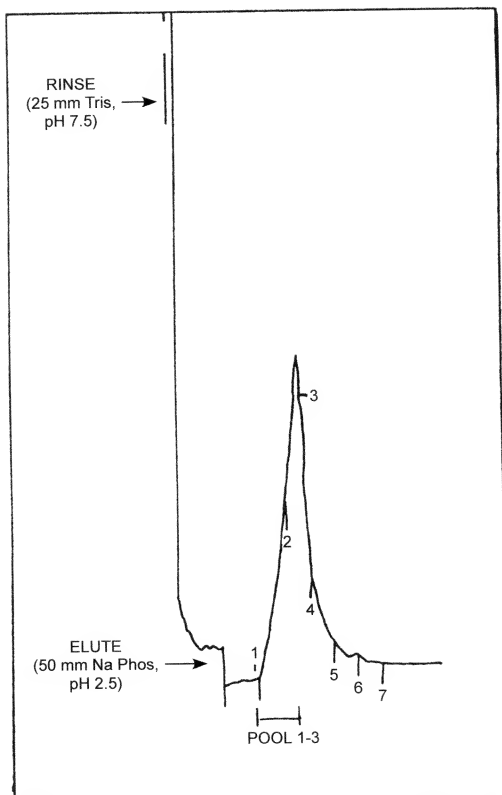
45 47 49 51 53 55 57 59 61 63 65





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FIG. 7





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FIG. 8A

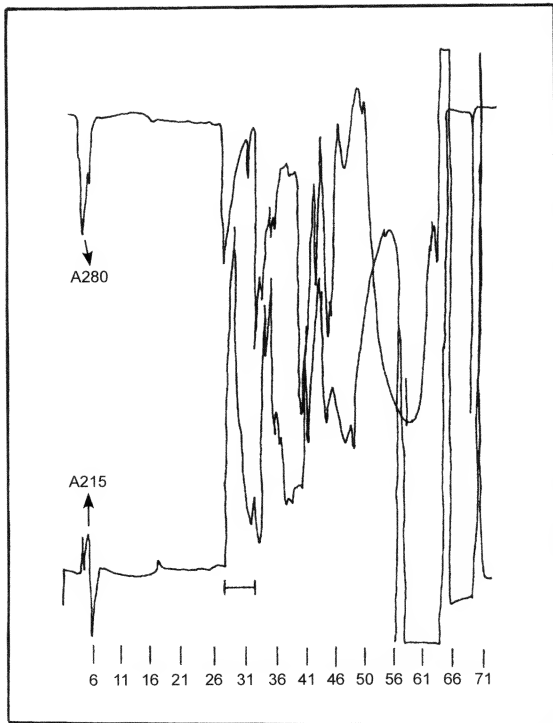
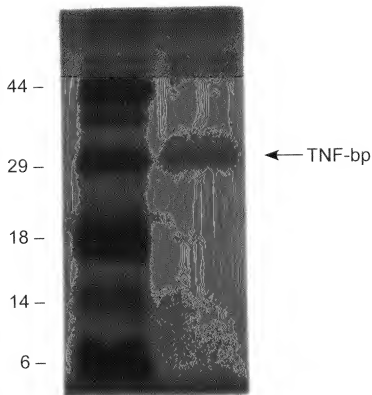


FIG. 8B





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FIG. 8C

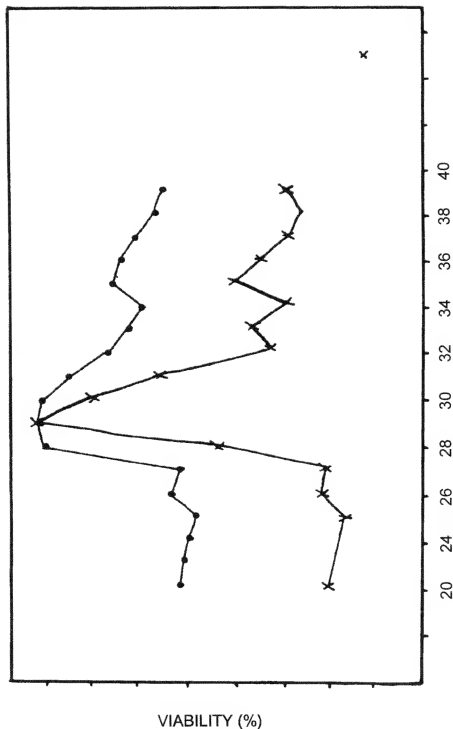


FIG. 9A

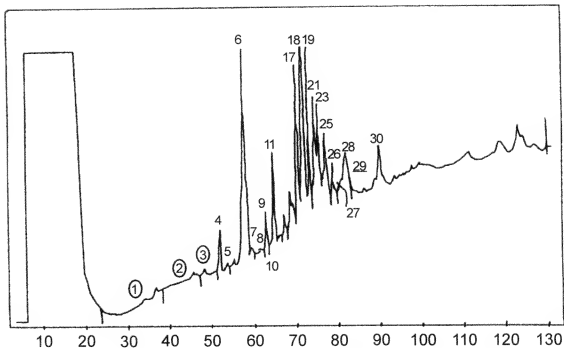
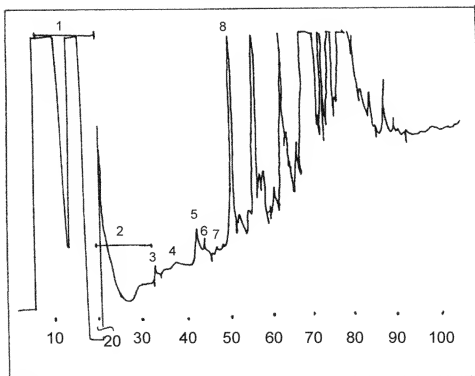


FIG. 9B-1





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FIG. 9B-2

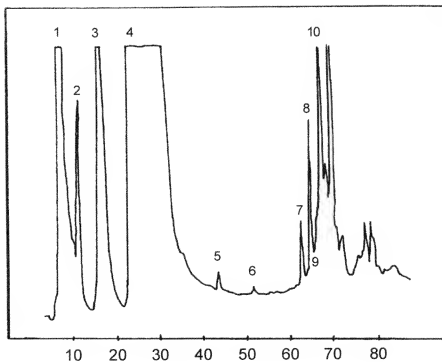
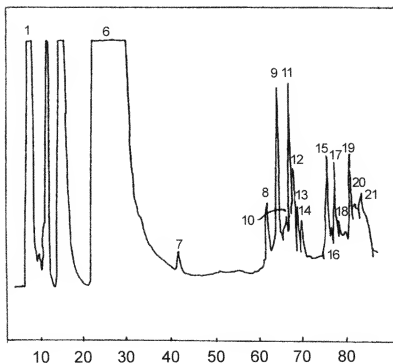


FIG. 9B-3





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FIG. 10A

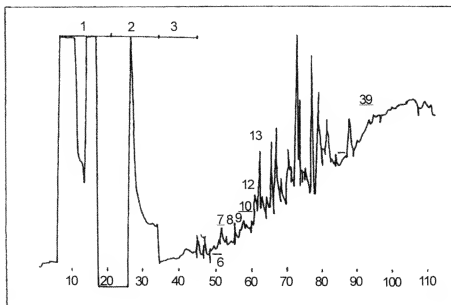
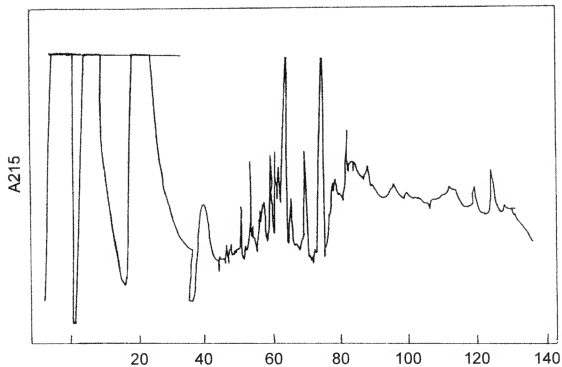


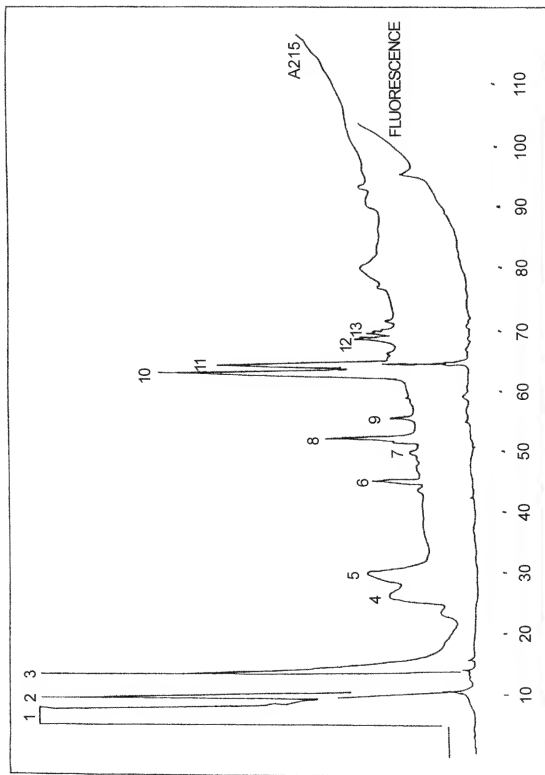
FIG. 10B





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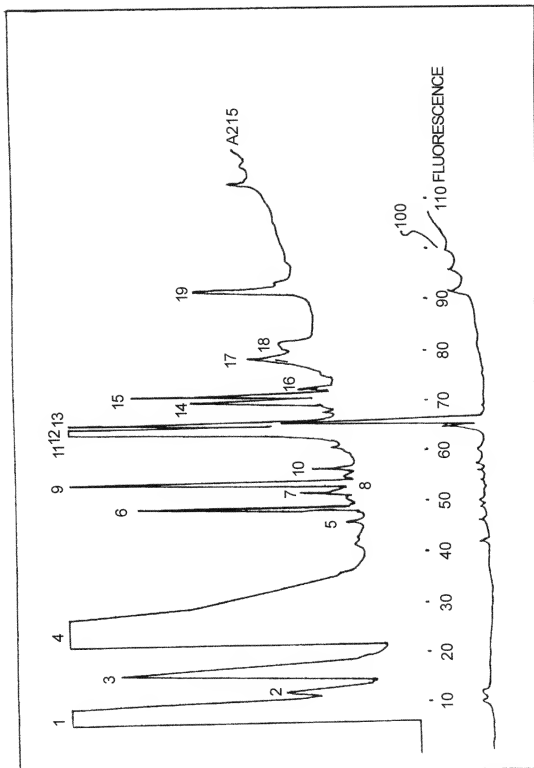
FIG. 11A





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FIG. 11B





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FIG. 12

4

A. * 20 * * * * *

D S V C P Q G K Y I H P Q N N S I C T K C H K G T Y L Y N D C P G P G Q D T D

60

* *

C _ _ _ S G S F T A S E N H L R H C L S C S _ _ K

B. * * * * *

(E) K Q N T V C T C H A G F F L R E N E C V S C (L) N C (K) (C) (L) (K) (E)

C. * *

(K) E M G Q V E I S S C T V D R R D T V C G C R K N (C) (Y) (R) (H) (Y)

D. *

(K) (S) L E C T K L C L P Q I E N
 (D)



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FIG. 13A

CATGCGCTGCA	GGTGCACACT	AGAGGATCTG	GGGCCITACTA	GCTTTTCAGITT	GAGGGAACA	AAATGAACA
80	90	100	110	120	130	140
AACAGGACAAC	TAGAACAAC	TTAAGCATCA	GATTGTATGC	CCCACTGTC	TAAGTTTCAA	GGAAGAATC
150	160	170	180	190	200	210
TAAACTTAGT	GAGTGGCGTG	GCCTGGCGG	AATGTTTCAC	TGAGGAAGGA	CTTGAGCCAG	GGAAGTTTTA
220	230	240	250	260	270	280
GATCTGCTAC	CCCTAAGCTT	CCCATCCCTC	CCTCTCTPTGA	TGGTGTCTCC	TCTATCTGAT	TCTTCCCCAG
289	298	307	316	325	334	
Val Leu Leu Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile Gly Leu Val	CTG CTG GAG CTG TTG GTG GGA ATA TAC CCC TCA GGG GTT ATT GGA CTG GTC					
343	352	361	370	379	388	
CCT CAC CTA GGG GAC AGG GAG AAG AGA GAT AGT GTG TGT CCC CAA GGA AAA TAT						
Pro His Leu Gly Asp Arg Glu Lys Arg Asp Ser Val Cys Pro Gln Gly Lys Tyr						



FIG. 13B

397	406	415	424	433	444
ATC CAC CCT CAA AAT AAT TCG ATT TGC TGT ACC AAG TGC CAC AAA G GTAGGGCAA					
Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys Ala					
454	464	474	484	494	504
GTGGAACGG TCAATGCCCT CAGGCTCTGG GTGCTGCTTC TTTCCTCTGCT TCTTCCAGTT GTTCTTCCT					
524	534	544	554	564	574
AACTTTGCTG TCTCTCCTGG GCTGGGATTT TCTCCCTCCC TCCTCTCTCTA GAGACTTCAG GGAATCGGCC					
594	604	614	624	634	644
CTGGCTGTTG TCCCTAGCAT GGGCTCCTT CCTTGTGTTT TCACCCGCAG CCTAACTCTG CGGCCCATTT					
664	673	682	691	700	
CA CA GGA ACC TAC TTG TAC AAT GAC TGT CCA GGC CCG GGG CAG GAT ACG GAC					
Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp					



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FIG. 13C

709	718	727	736	745	754
TGC AGG GAG TGT GAG AGC GGC TCC TTC ACC GCT TCA GAA AAC CAC CTC AGA CAC					
Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu Arg His					
763	772	781	797	807	817
TGC CTC AGC TGC TCC AAA TGC CGA AAG GGTGAGTGTG CACAGGCAGG AGAGTCAGGC					
Cys Leu Ser Cys Ser Lys Cys Arg Lys					
827	837	847	857	867	877
GGGTCTTGAG TGGTGTGTGG GTGCCTGTCT ATGTGCAGGC TGGTGGGTGT GGGCAGGAAG GTGTGTGTTT					
897	907	917	927	937	947
TGGTGGGACA CTGCATGGAT GTGAGTGTGT ATTACAGAGA CACACACTTA GGGGTATGTC AGGAAGGGGA					
967	977	987	997	1007	1016
TGCAGGGGACA GGAGGATGCA GGACTCATAC CCCATCTTCT CCCCTCACCA GAA ATG GGT CAG					
					Glu MET Gly Gln

1025

GTG GAG ATC
 Val Glu Ile



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FIG. 14

1	10	20	30	40	50	60	70	80
DSVCPQGYTHPQNN	SICCTKCHKGT	LYND	CFPGQD	TDCECE	SGSFTASE	NHLRHCL	SCSKCR	KEMGQVEIS
90								SCTVDRDT
VGCRKN								
KQNTVCTCHAGFF	FLRENECVSC							
LECTKLCLPQIEN								

FIG. 15

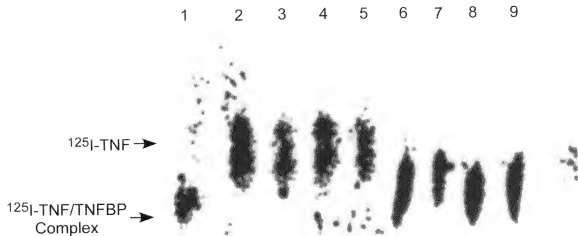


FIG. 16

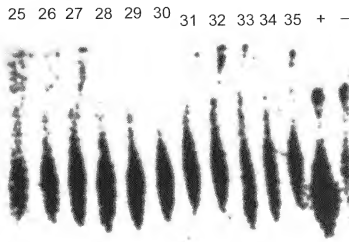


FIG. 17

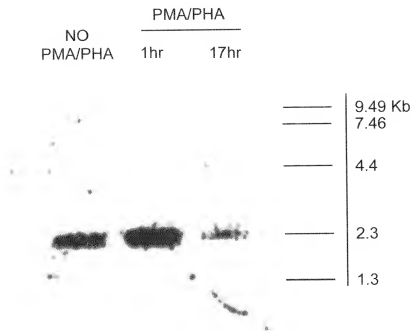


FIG. 18

11 21 51 12 22 52

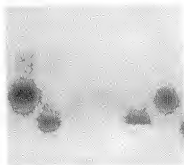




FIG. 19

20 Asp Ser Val Cys Pro Gln Gly Lys Tyr Ile His Pro Gln Asn Ser Ile Cys Cys Thr
40 Lys Cys His Lys Gly Thr Tyr Leu Tyr Asn Asp Cys Pro Gly Pro Gly Gln Asp Thr Asp
60 Cys Arg Glu Cys Glu Ser Gly Ser Phe Thr Ala Ser Glu Asn His Leu Arg His Cys Leu
80 Ser Cys Ser Lys Cys Arg Lys Glu Met Gly Gln Val Glu Ile Ser Ser Cys Thr Val Asp
100 Arg Asp Thr Val Cys Gly Cys Arg Lys Asn Gln Tyr Arg His Tyr Trp Ser Glu Asn Leu
120 Phe Gln Cys Phe Asn Cys Ser Leu Cys Ser Leu Asn Gly Thr Val His Leu Ser Cys Gln Glu
140 Lys Gln Asn Thr Val Cys Thr Cys His Ala Gly Phe Leu Arg Glu Asn Glu Cys Val
160 Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu Cys Thr Lys Leu Cys Leu Pro Gln Ile Glu
Asn



FIG. 20A

[illegible]



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FIG. 20B

531	540	549	558	567	576
GTG GAC CGG GAC ACC GTG	TGT GGC TGC AGG AAG	CAG TAC CGG CAT	TAT TGG		
Val Asp Arg Asp Thr Val Cys Gly Cys Arg Lys	Asn Gln Tyr Arg His Tyr Trp				
585	594	603	612	621	630
AGT GAA AAC CTT TTC CAG	TGC TTT AAT TGC AGC	CTC TGC CTT CAC	ACC GTG		
Ser Glu Asn Leu Phe Gln Cys Phe Asn Cys Ser	Leu Cys Leu Cys Leu Asn Gly Thr Val				
639	648	657	666	675	684
CAC CTC TCC TGC CAG GAG AAA	CAG AAC ACC GTG	TGC ACC TGC CAT	GCA GGT TTC		
His Leu Ser Cys Gln Glu Lys Gln Asn Thr Val	Cys Thr Cys His Ala Gly Phe				
693	702	711	720	729	738
TTT CTA AGA GAA AAC GAG TGT GTC	TCC TGT AGT AAC TGT	AAG AAA AGC CTG	GAG		
Phe Leu Arg Glu Asn Glu Cys Val Ser Cys Ser	Asn Cys Lys Ser Leu Glu				
747	756	765			
TGC ACG AAG TTG TGC CTA	CCC CAG ATT GAG AAT				
Cys Thr Lys Leu Cys Leu Pro Gln Ile Glu Asn					



FIG. 21A

10	20	30	40	50	60	70
GATCACTGG	ACCAGCCGT	GATCTTATG	CCCGAGTCTC	AACCCCTAAC	TGTCACCCCA	AGGCACCTGG
80	90	100	110	120	130	140
GACGTCCTGG	ACAGACCGAG	TCCCGGGAAG	CCCCAGCACT	GCCTGGTGCCA	CACTGCCCTG	AGCCCAATG
150	160	171	180	189	198	
GGGGACTGAG	AGGCCATAGC	TGTCCTGGC	ATG GGC CTC TCC ACC GTG CCT GAC CTG CTG			
			MET Gly Leu Ser Thr Val Pro Asp Leu Leu			
207	216	225	234	243	252	
CTG CCG CTG GTG CTC	GAG CTG TTG GTG GGA ATA TAC CCC TCA CGG GTT ATT					
Leu Pro Leu Val Leu Leu Glu Leu Leu Val Gly Ile Tyr Pro Ser Gly Val Ile						
261	270	279	288	297	306	
GGA CTG GTC CCT CTA GGG GAC AGG GAG AAG AGA GAT AGT GTG TGT CCC CAA						
Gly Leu Val Pro His Leu Gly Asp Arg Glu Lys Arg Asp Ser Val Cys Pro Gln						
315	324	333	342	351	360	
GGA AAA TAT ATC CAC CCT CAA AAT AAT TCG ATT TGC TGT ACC AAG TGC CAC AAA						
Gly Lys Tyr Ile His Pro Gln Asn Asn Ser Ile Cys Cys Thr Lys Cys His Lys						

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FIG. 21B

369	GGA ACC	TAC	TTG	TAC	AAT	GAC	TGT	CCA	GGC	CCG	GGG	CAG	GAT	ACG	GAC	TGC	AGG
	Gly Thr	Tyr	Leu	Tyr	Asn	Asp	Cys	Pro	Gly	Pro	Gly	Gln	Asp	Thr	Asp	Cys	Arg
423																	
	GAG TGT	GAG	AGC	GGC	TTC	TTC	ACC	GCT	TCA	GAA	AAC	CAC	CTC	AGA	CAC	TGC	CTC
	Glu Cys	Glu	Ser	Gly	Ser	Phe	Thr	Ala	Ser	Glu	Asn	His	Leu	Arg	His	Cys	Leu
477																	
	AGC TGC	TCC	AAA	TGC	CGA	AAG	GAA	ATG	GGT	CAG	GTG	GAG	ATC	TCT	TCT	TGC	ACA
	Ser Cys	Ser	Lys	Cys	Arg	Lys	Glu	MET	Gly	Gln	Val	Glu	Ile	Ser	Ser	Cys	Thr
531																	
	GTG GAC	CGG	GAC	ACC	GTG	TGT	GGC	TGC	AGG	AAG	AAC	CAG	TAC	CGG	CAT	TAT	TGG
	Val Asp	Arg	Asp	Thr	Val	Cys	Gly	Cys	Arg	Lys	Asn	Gln	Tyr	Arg	His	Tyr	Trp
585																	
	AGT GAA	AAC	CTT	TTC	CAG	TGC	TTC	AAT	TGC	AGC	CTC	TGC	CTC	AAT	GGG	ACC	GTG
	Ser Glu	Asn	Leu	Phe	Gln	Cys	Phe	Asn	Cys	Ser	Leu	Cys	Leu	Asn	Gly	Thr	Val
639																	
	CAC CTC	TCC	TGC	CAG	GAG	AAA	CAG	AAC	ACC	GTG	TGC	ACC	TGC	CAT	GCA	GGT	TTC
	His Leu	Ser	Cys	Gln	Glu	Lys	Gln	Asn	Thr	Val	Cys	Thr	Cys	His	Ala	Gly	Phe



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FIG. 21C

693	702	711	720	729	738
TTT CTA AGA GAA AAC GAG TGT GTC TCC TGT AGT AAC TGT AAG AAA AGC CTG GAG					
Phe Leu Arg Glu Asn Glu Cys Val Ser Cys Ser Cys Ser Asn Cys Lys Lys Ser Leu Glu					
747	750	765	774	783	792
TGC AGC AAG TTG TGC CTA CCC CAG ATT GAG AAT GTT AAG GGC ACT GAG GAC TCA					
Cys Thr Lys Leu Cys Leu Pro Gln Ile Glu Asn Val Lys Gly Thr Glu Asp Ser					
801	810	819	828	837	846
GGC ACC ACA GTG CTG TTG CCC CTG GTC ATT TTC TTT GGT CTT TGC CTT TTA TTC					
Gly Thr Thr Val Leu Leu Pro Leu Val Ile Phe Phe Gly Leu Cys Leu Leu Ser					
855	864	873	882	891	900
CTC CTC TTC ATT GGT TTA ATG TAT CGC TAC CAA CGG TGG AAG TCC AAG CTC TAC					
Leu Leu Phe Ile Gly Leu MET Tyr Arg Tyr Gln Arg Trp Lys Ser Lys Leu Tyr					
909	918	927	936	945	954
TCC ATT GTT TGT GGG AAA TCG ACA CCT GAA AAA GAG GGG GAG CTT GAA GGA ACT					
Ser Ile Val Cys Gly Lys Ser Thr Pro Glu Lys Glu Gly Leu Glu Gly Thr					
963	972	981	990	999	1008
ACT ACT AAG CCC CTG GCC CCA AAC CCA AGC TTC AGT CCC ACT CCA GGC TTC ACC					
Thr Thr Lys Pro Leu Ala Pro Asn Pro Ser Phe Ser Pro Thr Pro Gly Phe Thr					



FIG. 21D

1017	1026	1035	1044	1053	1062
CCC ACC CTG GGC TTC AGT CCC GTG CCC AGT TTC ACC TCC ACC TCC AGC TCC ACC					
Pro Thr Leu Gly Phe Ser Pro Val Pro Ser Thr Phe Thr Ser Ser Ser Thr					
1071	1080	1089	1098	1107	
1116					
TAT ACC CCC GGT GAC TGT CCC AAC TTT GCG GCT CCC CGC AGA GAG GTG GCA CCA					
Tyr Thr Pro Gly Asp Cys Pro Asn Phe Ala Ala Pro Arg Arg Glu Val Ala Pro					
1125	1134	1143	1152	1161	1170
CCC TAT CAG GGG GCT GAC CCC ATC CTT GCG ACA GCC CTC GCC TCC GAC CCC ATC					
Pro Tyr Gln Gly Ala Asp Pro Ile Leu Ala Thr Ala Leu Ala Ser Asp Pro Ile					
1179	1188	1197	1206	1215	1224
CCC AAC CCC CTT CAG AAG TGG GAG GAC AGC GCC CAC AAG CCA CAG AGC CTA GAC					
Pro Asn Pro Leu Gln Lys Trp Glu Asp Ser Ala His Lys Pro Gln Ser Leu Asp					
1233	1242	1251	1260	1269	1278
ACT GAT GAC CCC GCG ACG CTG TAC GCC GTG GTG GAG AAC GTG CCC CCG TTG CGC					
Thr Asp Asp Pro Ala Thr Leu Tyr Ala Val Val Glu Asn Val Pro Pro Leu Arg					
1287	1296	1305	1314	1323	1332
TGG AAG GAA TTC GTG CGG CCG CTA GGG CTG AGC GAC CAC GAG ATC GAT CGG CTG					
Trp Lys Glu Phe Val Arg Arg Leu Gly Leu Ser Arg His Glu Ile Asp Arg Leu					

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FIG. 21E

1341	1350	1359	1368	1377	1386
GAG CTG CAG AAC GGG CGC TGC CTG CGC GAG GCG CAA TAC AGC ATG CTG GCG ACC					
Glu Leu Gln Asn Gly Arg Cys Leu Arg Glu Ala Gln Tyr Ser MET Leu Ala Thr					
1395	1404	1413	1422	1431	1440
TGG AGG CCG CGC ACG CCG CGG CGC GAG GCC AGC CTG GAG CTG GGA CGC GTG					
Trp Arg Arg Arg Thr Pro Arg Arg Glu Ala Thr Leu Glu Leu Gly Arg Val					
1449	1458	1467	1476	1485	1494
CTC CGC GAC ATG GAC CTG CTG GGC TGC GAG GAG GAC ATC GAG GAG CCG CTT TGC					
Leu Arg Asp MET Asp Leu Leu Gly Cys Leu Glu Asp Ile Glu Glu Ala Leu Cys					
1503	1512	1521	1530	1546	1556
GGC CCC GCC GCC CTC CCG CCC CCG CCC AGT CTT CTC AGA TGA GGCTGCGCCC CTGGGGGCAG					
Gly Pro Ala Ala Leu Pro Pro Ala Pro Ser Leu Leu Arg					
1566	1576	1586	1596	1606	1616
CTCTAAGGAC CGTCTCTGCGA GATCGCCTTC CAACCCCACT TTTTCTGGA AAGGAGGGT CCTGCAGGGG					
1636	1646	1656	1666	1676	1686
CAAGCAGGAG CTAGCAGCG CCTACTTGGT GCTAACCCCT CGATGTACAT AGCTTTTCTC AGCTGCCCTGC					



FIG. 21F

1706	1716	1726	1736	1746	1756	1766
GGCCGCCGA	CAGTCAGCG	TGTGCGCG	GAGAGGTTG	CGCCGTGGC	TCAAGACCT	GAGTGGGTG
1776	1786	1796	1806	1816	1826	1836
TTTGCAGGA	TGAGGACGC	TATGCTCAT	GCCCGTTTG	GGTGCTCTCA	CCAGCAAGC	TGCTGGGGG
1846	1856	1866	1876	1886	1896	1906
CCCCGGTTC	GTCCCTGAGC	CTTTTTCACA	GTGCATAAGC	AGTTTTTTTT	GTTTTTGTTT	TGTTTTGTTT
1916	1926	1936	1946	1956	1966	1976
TGTTTTTAAA	TCAATCATGT	TACACTAATA	GAAACTTGGC	ACTCCTGTGC	CCTCTGCCTG	GACAAGCACA
1986	1996	2006	2016	2026	2036	2046
TAGCAAGCTG	AACTGTCTTA	AGGCAGGGC	GAGCACGAA	CAATGGGGCC	TTCAGCTGGA	GCTGTGGACT
2056	2066	2076	2086			
TTTGTACATA	CACATAAATT	CTGAAGTTAA	AGCTCAAAAA	AA		



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FIG. 22

GA ATT CCA CAA CGG TTT CCC TCT AGA AAT AAT TTT GTT TAA CTT TAA GAA GGA GAT ATA CAT

Start gene 10 protein

sequence

ATG GCT AGC ATG ACT GGT GGA CAG CAA ATG GGT ACG GAT CCG ATC TTG GAG GAT GAT TAA
Met Ala Ser Met Thr Gly Gly Gln Met Gly Thr Asp Pro Ile Leu Glu Asp Asp stop
Translational coupler

ATG GAC AGC GTT TGC CCC

Met Asp Ser Val Cys Pro

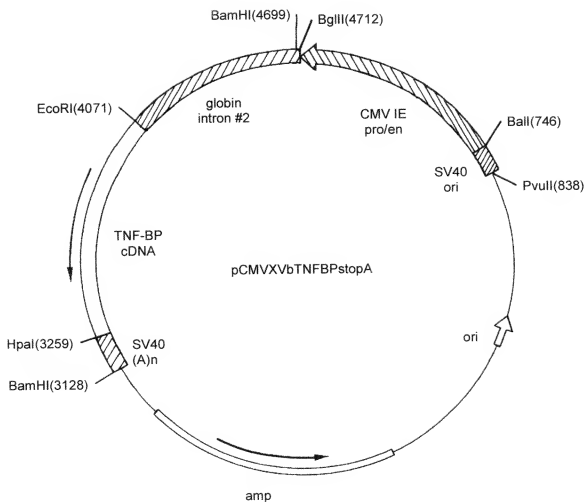
Start TNF inhibitor

sequence



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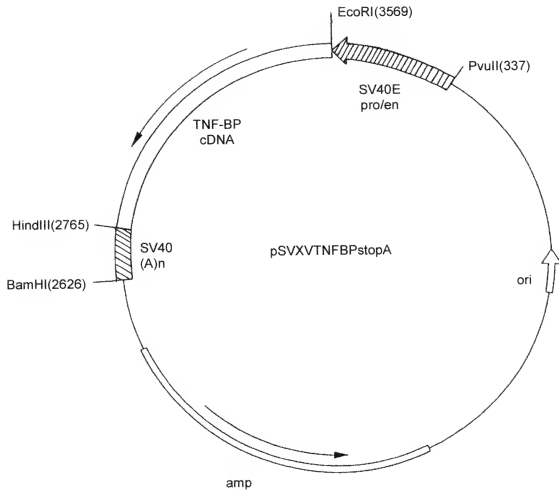
FIG. 23





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FIG. 24





Inventor: Brewer et al.
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FIG. 25

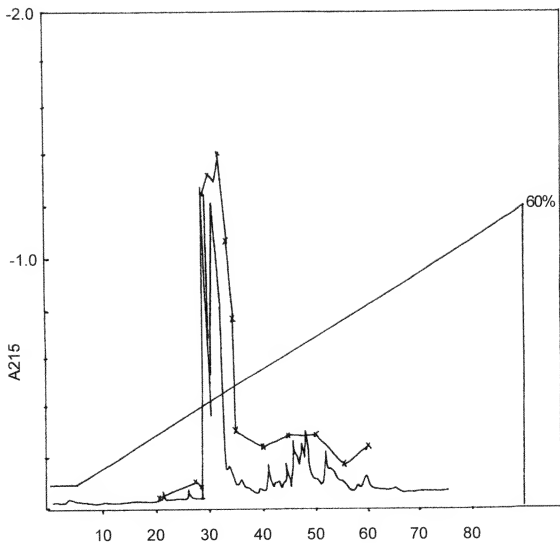
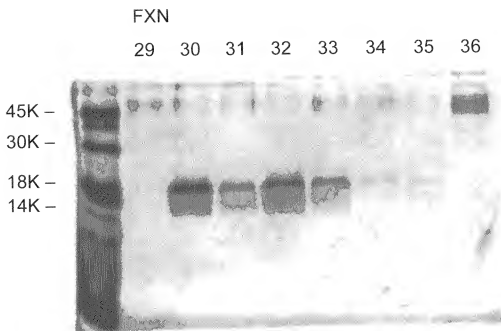


FIG. 26





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FIG. 27

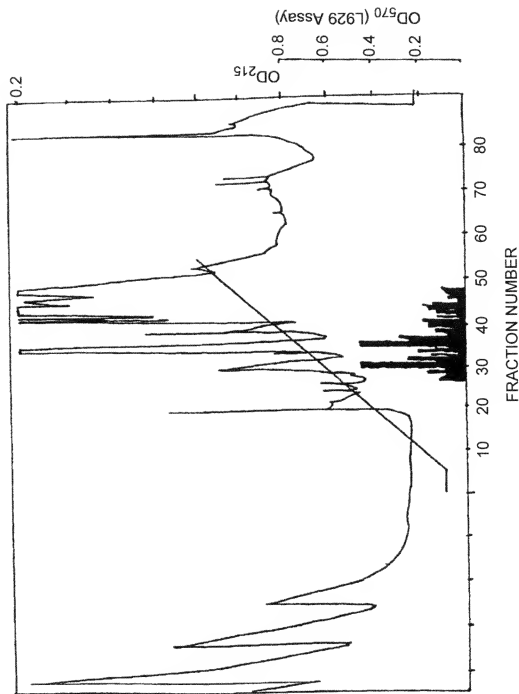
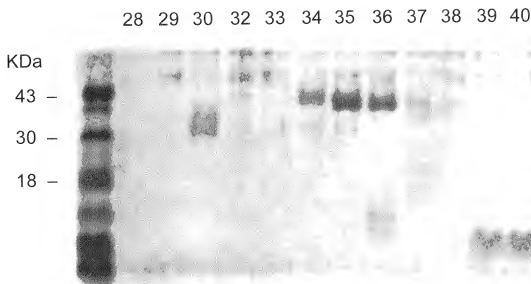


FIG. 28





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FIG. 29

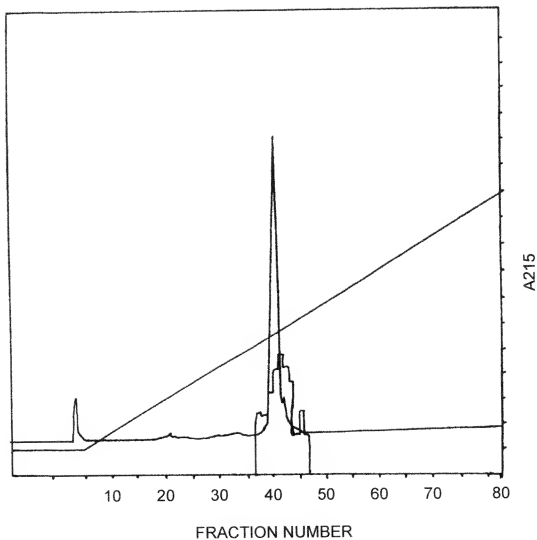
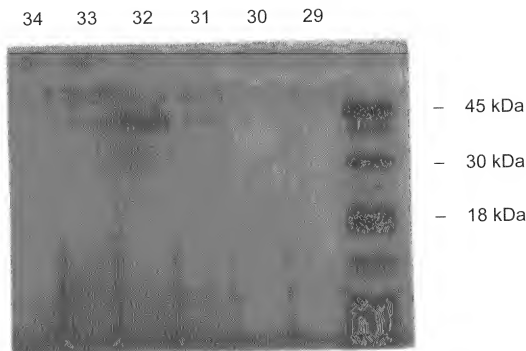


FIG. 30





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FIG. 31

U937-derived TNF inhibitor1 (30 kDa)

()-()-Val-()-Pro-Gln-Gly-Lys-Tyr-Ile-His-Pro-Gln-()-Asn-()-Ile-

U937-derived TNF inhibitor2 (40 kDa)

Leu-Pro-Ala-Gln-Val-Ala-Phe-Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr-Cys-Arg-
Leu-Arg-Glu-Tyr-Tyr-Asp-Gln-Thr-Ala-Gln-Met-Cys-Cys-Ser-Lys-Cys-

Urine-derived TNF inhibitor2 (40 kDa)

Ala-Gln-Val-Ala-Phe-Thr-Pro-Tyr-Ala-Pro-Glu-Pro-Gly-Ser-Thr-Cys-()-Leu-()-
Glu-



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FIG. 34

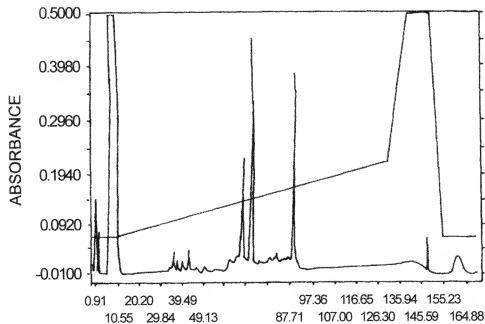


FIG. 35

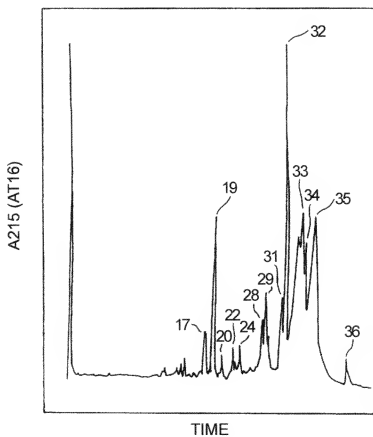
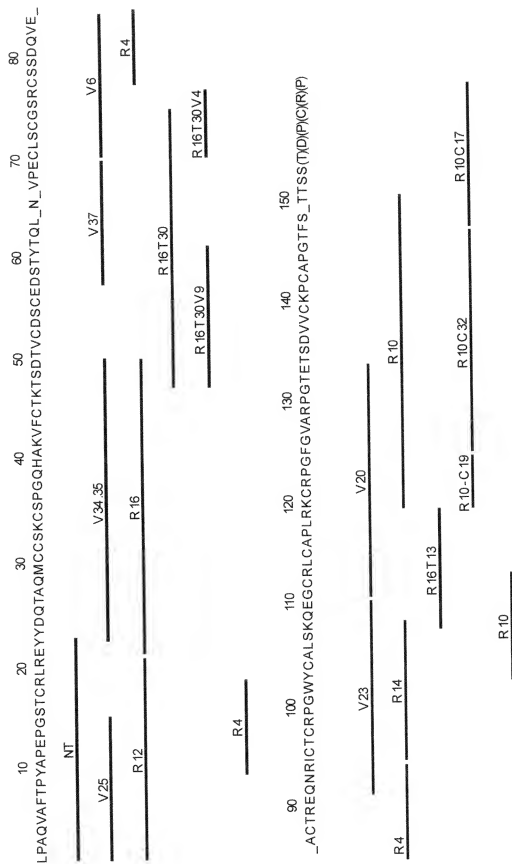




FIG. 36



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FIG. 37

236	245	254	263	272	281	227
CCG GAG CCC GGG AGC ACA TGC CGG CTC AGA GAA TAC	Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp					
236	245	254	263	272	281	227
CCAG ACA GCT CAG ATG TGC TGC AGC AAG TGC TCG CCG GGC CAA CAT GCA AAA GTG	Thr Ala Gln MET Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val					
290	299	308	317	326	335	
TTT ACC ACC TGC GAC ACC GTG TGT TGT TCC TGT TGT GAG GAC AGC ACA TAC	Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr					
344	353	362	371	380	389	
ACC CAG CTC TGG AAC TGG GTT CCC GAG TGC TGC AGC TGT GGC TCC CGC TGT AGC	Thr Thr Gln Leu Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser					
398	407	416	425	434	443	
TCT GAC CAG GTG GAA ACT CAA GCC TGC ACT CCG GAA CAG AAC CGC ATC TGC ACC	Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys Thr					
452	461	470				
TGC AGG CCC GGC TGG TAC TGC	Cys Arg Pro Gly Trp Tyr Cys					



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FIG. 38

Leu Pro Ala Gln Val Ala Phe Thr Pro Tyr Ala Pro Glu Pro Gly Ser
Thr Cys Arg Leu Arg Glu Tyr Tyr Asp Gln Thr Ala Gln Met Cys Cys
Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val Phe Cys Thr Lys Thr
Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr Thr Gln Leu
Trp Asn Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser Ser
Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys
Thr Cys Arg Pro Gly Trp Tyr Cys Ala Leu Ser Lys Gln Glu Gly Cys
Arg Leu Cys Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala
Arg Pro Gly Thr Glu Thr Ser Asp Val Val Cys Lys Pro Cys Ala Pro
Gly Thr Phe Ser Asn Thr Thr Ser Ser Thr Asp Ile Cys Arg Pro His
Gln Ile Cys Asn Val Val Ala Ile Pro Gly Asn Ala Ser Arg Asp Ala
Val Cys Thr Ser Thr Ser Pro Thr Arg Ser Met Ala Pro Gly Ala Val
His Leu Pro Gln Pro Val Ser Thr Arg Ser Gln His Thr Gln Pro Thr
Pro Glu Pro Ser Thr Ala Pro Ser Thr Ser Phe Leu Leu Pro Met Gly
Pro Ser Pro Pro Ala Glu Gly Ser Thr Gly Asp



FIG. 39A

10	20	30	40	50	60	70
GAATTGGCG	CAGCGAGCC	TGGAGAGAAG	GGCTGGGCT	GCGAGGGCGC	GAGGCGCGA	GGGAGGGGG
80	90	101	110	119		
CAACCGGACC	CGGCCCGCAC	CC ATG GCG CCC GTC	GCC GTC TGG GCC GCG CTG GCC			
		MET Ala Pro Val Ala Val Trp Ala Ala Leu Ala				
128	137	146	155	164	173	
GTC GGA CTG GAG CTC TGG GGT GCG GCG CAC GCC	TTG CCC GCG GTC GCG GCG GCA GTG GCA TTT					
Val Gly Leu Glu Leu Trp Ala Ala His Ala Leu Pro Ala Gln Val Ala Phe						
182	191	200	209	218	227	
ACA CCC TAC CCC CCS GAG CCC AGC ACA ICC CGG CTC ABA BAA TAC TAT SAC						
Thr Pro Tyr Ala Pro Glu Pro Gly Ser Thr Cys Arg Leu Arg Glu Tyr Tyr Asp						
236	245	254	263	272	281	
CAG ACA GCT CAG ATG TGC TGC AGC AAG TGC TCG GGC CAA CAT GCA AAA GTC						
Gln Thr Ala Gln MET Cys Cys Ser Lys Cys Ser Pro Gly Gln His Ala Lys Val						
290	299	308	317	326	335	
TTC TGT ACC AAG ACC TCG GAC ACC GTG TGT GAC TTC TGT GAG GAC AGC ACA TAC						
Phe Cys Thr Lys Thr Ser Asp Thr Val Cys Asp Ser Cys Glu Asp Ser Thr Tyr						

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FIG. 39B

344	353	362	371	380	389
ACC CAG CTC TGG AAC TGG GTT CCC GAG TGC TTG AGC TGT GGC TCC CGC TGT AGC					
Thr Gln Leu Trp Asp Trp Val Pro Glu Cys Leu Ser Cys Gly Ser Arg Cys Ser					
398	407	416	425	434	443
TCT GAC CAG GTG GAA ACT CAA GCC TGC ACT CGG GAA CAG AAC CGC ATC TGC ACC					
Ser Asp Gln Val Glu Thr Gln Ala Cys Thr Arg Glu Gln Asn Arg Ile Cys Thr					
452	461	470	479	488	497
TGC AGG CCC GGC TGG TAC TGC GCG CTG AGC AAG CAG GAG GGG TGC CGG CTG TGC					
Cys Arg Pro Gly Trp Tyr Cys Ala Leu Ser Lys Glu Gly Cys Arg Leu Cys					
506	515	524	533	542	551
GCG CCG CTG CGC AAG TGC CCG CCG GGC TTC GGC CTG GCC AGA CCA GGA ACT GAA					
Ala Pro Leu Arg Lys Cys Arg Pro Gly Phe Gly Val Ala Arg Pro Gly Thr Glu					
560	569	578	587	596	605
ACA TCA GAC GTG GTG TGC AAG CCC TGT GCC CCG GGG AGC TTC TCC AAC ACG ACT					
Thr Ser Asp Val Val Cys Lys Pro Cys Ala Pro Gly Thr Phe Ser Asn Thr Thr					



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FIG. 39C

614	623	632	641	650	659												
TCA	TCC	ACG	GAT	ATT	TGC	AGG	CCC	CAC	CAG	ATC	TGT	AAC	GTG	GTG	GCC	ATC	CCT
Ser	Ser	Thr	Asp	Ile	Cys	Arg	Pro	His	Gln	Ile	Cys	Asn	Val	Val	Ala	Ile	Pro
668	677	686	695	704	713												
GGG	AAT	GCA	AGC	AGG	GAT	GCA	GTC	TGC	ACG	TCC	ACG	TCC	CCC	ACC	CGG	AGT	ATG
Gly	Asn	Ala	Ser	Arg	Asp	Ala	Val	Cys	Thr	Ser	Thr	Ser	Pro	Thr	Arg	Ser	MET
722	731	740	749	758	767												
GCC	CCA	GGG	GCA	GTA	CAC	TTA	CCC	CAG	CCA	GTG	TCC	ACA	CGA	TCC	CAA	CAC	ACG
Ala	Pro	Gly	Ala	Val	His	Leu	Pro	Gln	Pro	Val	Ser	Thr	Arg	Ser	Gln	His	Thr
776	785	794	803	812	821												
CAG	CCA	ACT	CCA	GAA	CCC	AGC	ACT	GCT	CCA	AGC	ACC	TCC	TTC	CTG	CTC	CCA	ATG
Gln	Pro	Thr	Pro	Glu	Pro	Ser	Thr	Ala	Pro	Ser	Thr	Ser	Phe	Leu	Leu	Pro	MET
830	839	848	857	866	875												
GGC	AGC	CCC	CCA	GCT	GAA	GGG	AGC	ACT	GGC	GAC	TTC	GCT	CTT	CCA	GTT	GGA	Gly
Gly	Pro	Ser	Pro	Ala	Glu	Gly	Ser	Thr	Gly	Asp	Phe	Ala	Leu	Pro	Val	Gly	



FIG. 39D

884	893	902	911	920	929
CTG ATT GTG GGT GTG ACA GCC TTG GGT CTA ATA ATA GGA GTG AAC TGT					
Leu Ile Val Gly Val Thr Ala Leu Gly Leu Ile Ile Gly Val Val Asn Cys					
938	947	956	965	974	983
GTC ATC ATG ACC CAG GTG AAA AAG AAG CCC TTG TGC CTG CAG AGA GAA GCC AAG					
Val Ile MET Thr Gln Val Lys Lys Pro Leu Cys Leu Gln Arg Glu Ala Lys					
992	1001	1010	1019	1028	1037
GTG CCT CAC TTG CCT GCC GAT AAG GCC CGG GGT ACA CAG GGC CCC GAG CAG CAG					
Val Pro His Leu Pro Ala Asp Lys Ala Arg Gly Thr Gln Gly Pro Glu Gln Gln					
1046	1055	1064	1073	1082	1091
CAC CTG CTG ATC ACA GCG CCG AGC TCC AGC AGC AGC TCC CTG GAG AGC TCG GCC					
His Leu Leu Ile Thr Ala Pro Ser Ser Ser Ser Ser Ser Leu Glu Ser Ser Ala					
1100	1109	1118	1127	1136	1145
AGT GCG TTG GAC AGA AGG GCG CCC ACT CGG AAC CAG CCA CAG GCA CCA GGC GTG					
Ser Ala Leu Asp Arg Arg Ala Pro Thr Arg Asn Gln Pro Gln Ala Pro Gly Val					

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FIG. 39E

1154	1163	1172	1181	1190	1199
GAG GCC AGT GGG GCC GGG GAG GCC AGC ACC GGG AGC TCA GAT TCT TCC	Glu Ala Ser Gly Ala Gly Glu Ala Arg Ala Ser Thr Gly Ser Ser Asp Ser Ser				
1208	1217	1226	1235	1244	1253
CCT GGT GGC CAT GGG ACC CAG GTC AAT GTC ACC TGC ATC GTG AAC GTC TGT AGC	Pro Gly Gly His Gly Thr Gln Val Thr Cys Ile Val Asn Val Cys Ser				
1262	1271	1280	1289	1298	1307
AGC TCT GAC CAC AGC TCA CAG TGC TCC TCC CAA GCC AGC TCC ACA ATG GGA GAC	Ser Ser Asp His Ser Ser Gln Cys Ser Ser Gln Ala Ser Ser Thr MET Gly Asp				
1316	1325	1334	1343	1352	1361
ACA GAT TCC AGC CCC TCG GAG TCC CCG AAG GAC GAG CAG GTC CCC TTC TCC AAG	Thr Asp Ser Ser Pro Ser Glu Ser Pro Lys Asp Glu Gln Val Pro Phe Ser Lys				
1370	1379	1388	1397	1406	1415
GAG GAA TGT GCC TTT CGG TCA CAG CTG GAG ACG CCA GAG ACC CTG CTG GGG AGC	Glu Glu Cys Ala Phe Arg Ser Gln Leu Glu Thr Pro Glu Thr Leu Leu Gly Ser				



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FIG. 39F

1424	1433	1442	1451	1460	1469
ACC GAA GAG AAG CCC CTG CCC CTT GGA GTG CCT GAT GCT GGG ATG AAG CCC AGT					
Thr Glu Glu Lys Pro Leu Pro Leu Gly Val Pro Asp Ala Gly MET Lys Pro Ser					
1478	1488	1498	1508	1518	1528
1538					
TAA CCAGGCCGGT GTGGGCTGTG TCGTAGCCAA GGTGGGCTGA GCCCTGGCAG GATGACCCCTG					
1548	1558	1568	1578	1588	1598
CGAAGGGGCC CTGGTCCTTC CAGGCCCCCA CCACTAGGAC TCTGAGGCTC TTCTCTGGCC AAGTTCCTCT					
1618	1628	1638	1648	1658	1668
AGTGCCTCC ACAGCCGCGAG CCTCCCTCTG ACCTGCAGGC CAAGAGCAGA GGCAGCGGT TGTGGAAGC					
1688	1698	1708	1718	1728	1738
CTCTGCTGCC ATGTTGTGTC CCTCTCGGAA GGCTGGCTGG GCATGGACGT TCGGGGCATG CTGGGGCAAG					
1758	1768	1778	1788	1798	1808
TCCCTGACTC TCTGTGACCT GCCCGGCCCA GCTGCACCTG CCAGCCTGSC TTCTGGAGCC CTTGGGTTTT					
1818					



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FIG. 39G

1828	1838	1848	1858	1868	1878	1888
TTGTTTGTTT	GTTCGTTTGT	TTGTTTGTTT	CTCCCCCTGG	GCTCTGCCCC	AGCTCTGGCT	TCCAGAAAAAC
1898	1908	1918	1928	1938	1948	1958
CCCAGCATCC	TTTTCTGCAG	AGGGGCTTTC	TGGAGAGGAG	GGATGCTGCC	TGAGTCACCC	ATGAAGACAG
1968	1978	1988	1998	2008	2018	2028
GACAGTGCTT	CAGCCTGAGG	CTGAGACTGC	GGGATGGTCC	TGGGGGCTCTG	TGCAGGGAGG	AGGTGGCAGC
2038	2048	2058	2068	2078	2088	2098
CCTGTAGGGA	ACGGGGTCTT	TCAAGTTAGC	TCAGGAGGCT	TGGAAAAGCAT	CACCTCAGGC	CAGGTGCAGT
2108	2118	2128	2138	2148	2158	2168
CCCTCACGCC	TATGATCCCA	GCACTTTGGG	AGGCTGAGGC	GGGTGGATCA	CCTGAGGTTA	GGAGTTGCAG
2178	2188	2198	2208	2218	2228	2238
ACCAGCCTGG	CCAACATGTT	AAAACCCCAT	CTCTACTAAA	AATACAGAAA	TTAGCCGGGC	GTGTTGGCGG



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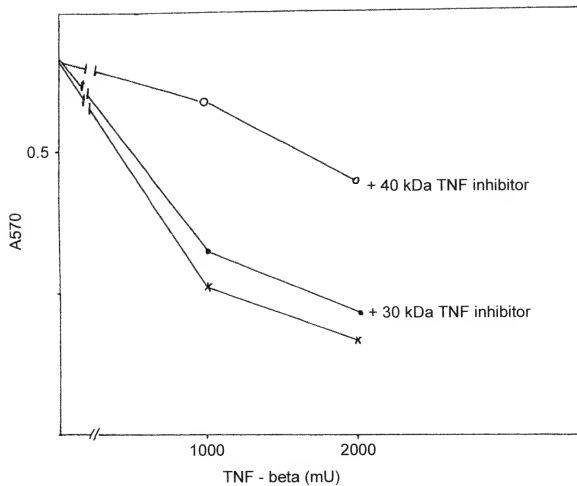
FIG. 39H

2248	2258	2268	2278	2288	2298	2308
GCACCTATAG	TCCCAGCTAC	TCAGAGCCT	GAGCTGGGA	AATCGTTTGA	ACCCGGAAG	CGGAGTTTC
2318	2328	2338	2348	2358	2368	2378
AGGGAGCCGA	GATCAGCCA	CTGCACTCCA	GCCTGGGCGA	CAGAGCGAGA	GTCTGTCTCA	AAAGAAAAA
2388						
AAAAAAAAAC GAATTC						



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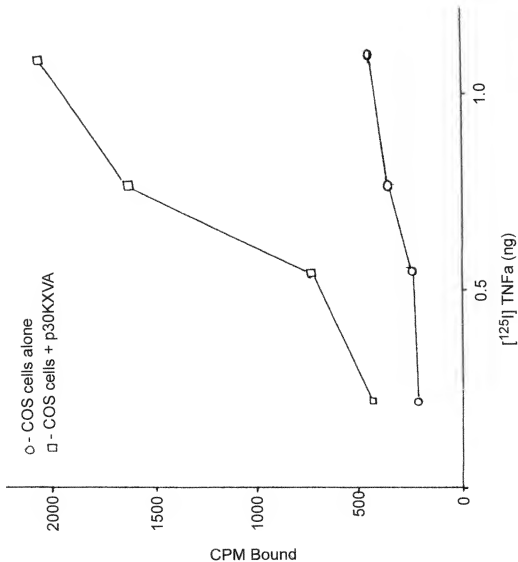
FIG. 40





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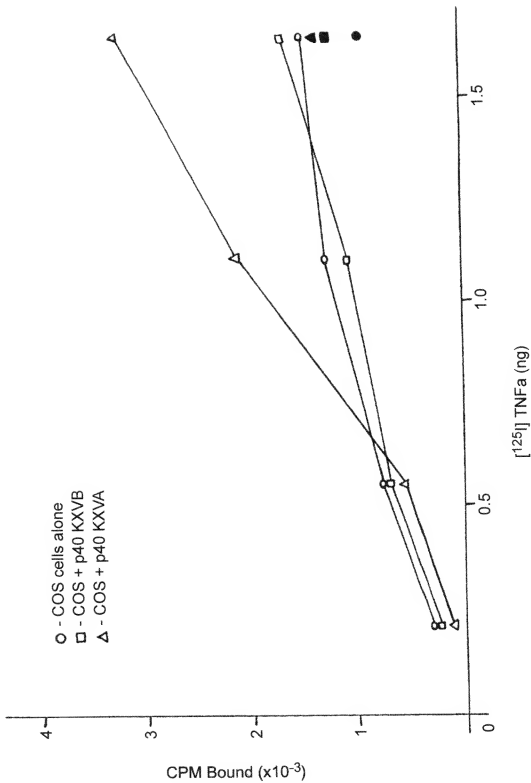
FIG. 41





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FIG. 42





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FIG. 43

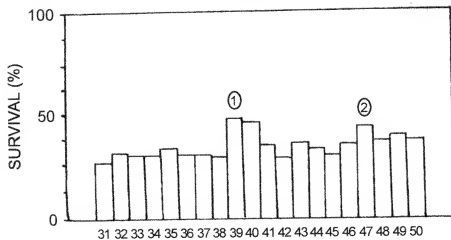


FIG. 44A

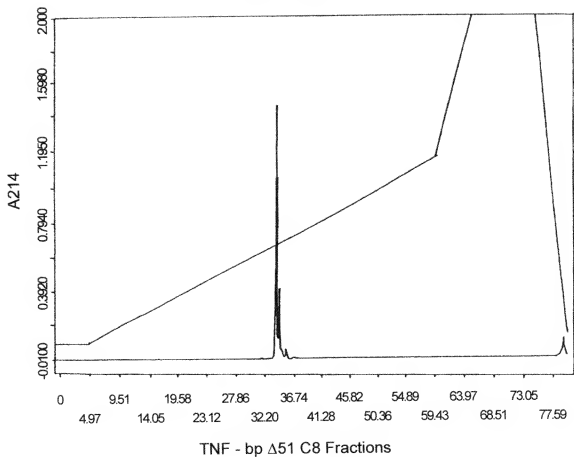
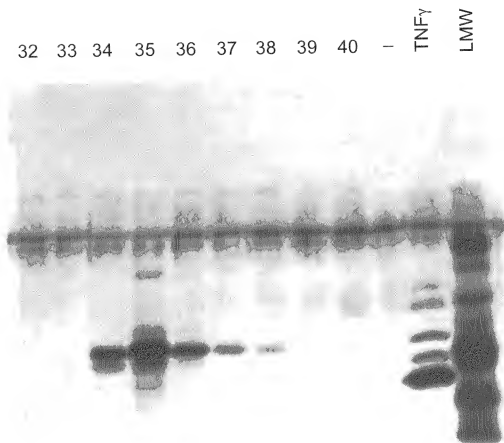


FIG. 44B





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FIG. 44C

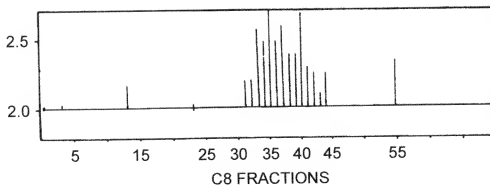


FIG. 45A

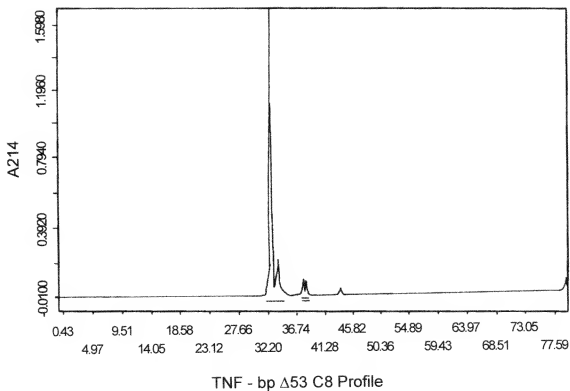
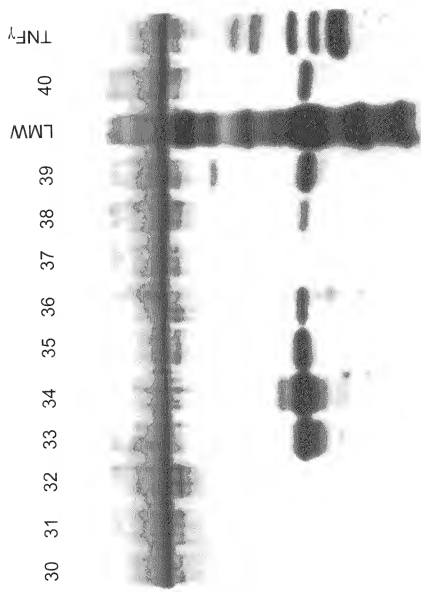


FIG. 45B





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FIG. 45C

